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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/881,635	06/14/2001	Peter M. Price	D6302	7258

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	9

DATE MAILED: 01/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/881,635	PRICE ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2002*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,6 and 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,6 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on October 31, 2002, as Paper No. 8. Claims 1, 3, 5, 6 and 8 have been amended. Claims 2, 4, 7, 9 and 10 have been cancelled. Claims 1, 3, 5, 6 and 8 are pending in the application and are examined herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action.

3. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 3, 5, 6 and 8 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for treating or preventing a pathological state of the kidney in an individual wherein said state is characterized by an undesirable level of cyclin-dependent kinase inhibitor activity in the kidney, wherein the method comprises the step of reducing or eliminating the expression of the p21 gene in said kidney of said individual. The amendment limits the scope of the claims to treating or preventing a pathological state of a

kidney by reducing or eliminating the expression of the p21 gene. However, the claims still contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons set forth in the previous Office Action.

The claims are still very broad and encompass treating or preventing any pathological state of a kidney by reducing or preventing the expression of the p21 gene in the kidney. Therefore, the broadest claims encompass treating or preventing renal fibrosis, glomerulosclerosis, reduced filtration rates, hypertension, rejection of kidney transplants, kidney cancer, etc. Furthermore, the method encompasses reducing or eliminating the expression the p21 gene by administering any compound that reduces or eliminates p21 gene expression. Therefore, the broadest claims encompass administering a broad genus of therapeutic agents including a gene therapy construct that expresses an inhibitor of p21 expression, antisense molecules which inhibit the translation of p21, chemical compounds which reduce the expression of the p21 gene, etc.

As mentioned in the previous Office Action, the relevant art considered gene therapy and antisense therapy methods to be unpredictable, and regarding treating organ transplant rejection, the relevant prior art contemplates increasing p21 expression to treat organ transplant rejection—not decreasing p12 expression, as contemplated by the instant application (see previous Office Action, p. 6 second paragraph). It was also noted that there are no working examples in the specification indicating that reducing or eliminating p21 expression would have any therapeutic effect on any pathophysiological state of the kidney. It was also noted that the specification indicates that transgenic mice which do not express p21 (i.e. p21 knock-out mice) were resistant

to the functional and morphologic consequences of partial renal ablation. However, there are no working examples or guidance indicating that an animal which expresses p21 can be administered any therapeutic molecule to reduce or eliminate p21 expression in the animal. No known molecules have been identified which could be administered to an animal and completely eliminate the expression of any gene. Furthermore, the specification does not specifically indicate any such molecules other than to merely state, "reduction or elimination of p21 expression is performed by techniques such as drug therapy, genetic manipulation, or antisense DNA, etc." (See p. 9, lines 8-10 of the specification).

Considering the breadth of the claims and the lack of working examples or guidance in the specification, the quantity of experimentation in this area is considered to be extremely large since determination of the efficacy of treatment would require, initially, the identification of therapeutic molecules in animal models. Gene therapy, antisense therapy, and other therapeutic molecules would have to be produced and tested in animals for efficacy. This would require making and testing the therapeutic molecules and testing the therapeutic molecules in vitro, followed by testing in animal models to show that the treatment can overcome the problems recognized in the art (mentioned above, and in the previous Office Action). Therefore for the reasons mentioned above and the reasons set forth in the previous Office Action, the amount of additional experimentation required to make and use the invention is considered to be undue.

Response to Arguments

6. Applicant's arguments filed October 31, 2002 have been fully considered but they are not persuasive. Applicants disagree with the assertion that gene therapy and antisense therapy are unpredictable. Applicants contend that there has been ample groundwork laid in the field of

gene therapy and antisense therapy to guide of or ordinary skill in the art in practicing the claimed invention. Applicants refer to the cited references (Anderson and Branch) which indicate that over 300 clinical protocols involving gene therapy have been approved in the US, and also predicts that gene therapy should produce statistically significant data within 5 years showing that gene therapy can help improve the condition of patients (see p. 6 of the response). Applicants also indicate that gene therapy has been successful for treating severe combined immunodeficiency disease and sickle cell anemia. Applicants also point out that the cited reference (Branch) indicates that the specificity of antisense therapy will increase as strategies are optimized and advances bring fewer side effects (see p. 6 of the response). Finally, Applicants contend that mice expressing a homozygous null mutation in p21 are clearly demonstrated to be highly resistant to the deleterious effects of renal ablation and that this allows the reasonable prediction that reducing or eliminating p21 gene expression will be able to ameliorate or prevent the effects of acute renal stress or chronic renal failure (see paragraph bridging p. 7-8 of the response.

In response, it is acknowledged that the specification does indicate that a mouse comprising a null mutation of the p21 gene is resistant to the deleterious effects of renal ablation. However, the examiner respectfully points out that the specification does not indicate any workable example how to reduce or eliminate p21 expression in an individual. In order to be perfectly clear, the relevant issues are: 1) Many different mechanisms are involved in the development of kidney disorders; therefore, reducing or eliminating p21 gene expression may not treat every kidney disorder; 2) the p21 knock-out mouse is not a proper animal model for the

claimed therapy; and 3) methods for efficiently reducing or eliminating the expression of p21 in a kidney are unpredictable.

With respect to reducing or eliminating p21 for treating or preventing any pathophysiological state of the kidney, it is noted that many different processes are involved in the development of kidney disorders such as renal fibrosis, glomerulosclerosis and renal failure. For instance, el Nahas et al. (Int. J. Biochem. Cell Biol. 1997; 29:55-62) teaches,

> "The progression of chronic renal failure is characterised histologically by glomerulosclerosis, tubulointerstitial fibrosis and vascular sclerosis. Recent research has identified common mechanisms underlying these fibrotic processes. In particular, the scarring process within the glomeruli and the tubulointerstitium involves the infiltration by inflammatory cells including monocytes, the activation of intrinsic renal cells as well as interactions between infiltrating and resident cells. These interactions depend, to a large extent, on the release by these cells of chemokines, cytokines and growth factors. These factors are in turn involved in the induction of cellular proliferation within the kidney and the stimulation of the synthesis and deposition of extracellular collagenous matrix. Fibrosis is believed to result from excessive synthesis of extracellular matrix and a concommitant decrease in its breakdown." (See abstract)

It is clear that the many different mechanisms are involved in the development of kidney pathologies. Many of these mechanisms are not known to involve p21. For instance, there is no evidence that p21 is involved in matrix breakdown, or the release of chemokines, cytokines and growth factors. Therefore, it is unlikely that that reducing or eliminating p21 in the kidney would result in blocking every pathway that leads to kidney disorder—making it unlikely that reducing or eliminating p21 gene expression would be an effective treatment for every kidney disorder.

With respect to the p21 knock mouse as an animal model for the claimed therapy, it is noted that a mouse comprising a null mutation in its genome cannot be correlated to administering an inhibitor of gene expression (such as a drug, gene therapy construct, or

antisense molecule) to an animal. Producing a knockout animal encompasses making a disruption in a particular gene at the chromosomal level. The instant invention only encompasses administering a therapeutic compound (such as a gene therapy vector, antisense DNA, drug, etc.) to an animal in order to inhibit the expression of a particular gene. There are several known problematic issues associated with administering a therapeutic compound to an animal. For instance, methods of delivery, the immune response, as well as compound stability are all critical factors associated with administering a therapeutic compound to an animal. An animal having a null mutation in a gene has none of these issues. Therefore, one cannot reasonably correlate a knockout animal to methods for inhibiting gene expression in an animal. The knockout animal is, therefore, not an accepted animal model for the claimed therapeutic method.

Regarding the unpredictable nature of methods for efficiently reducing or eliminating the expression of a gene in an animal, it is noted that the specification contemplates drug therapy, gene therapy, antisense DNA, etc. for reducing or eliminating p21 expression. However, the specification does not specifically identify any drugs, antisense molecules, or gene therapy methods which can be used. As mentioned in the previous Office Action and summarized above, the relevant art recognizes the unpredictable nature of gene therapy and antisense therapy. Applicants contend that gene therapy and antisense therapy are enabled, but do indicate any evidence which specifically indicates that gene therapy or antisense therapy can be used to reduce or eliminate p21 expression in a kidney of an animal. It is noted that MPEP 716.01(c) indicates,

> "The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success,

solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant."

Furthermore, p21 is a complex molecule with multiple functions including regulation of cell cycle control, DNA synthesis, apoptosis, and stem cell commitment differentiation. The functions of p21 are modulated through direct and indirect interactions with many different proteins (including cyclin, CDK, c-myc, PCNA, E2F, caspase 3, calmodulin, CK2, KF-kB, p300, etc.) (See Dotto; p. M49, Figs. 3 and 4). However, the specification (and prior art) does not specifically identify how p21 reduces the effect of renal ablation, other than speculating that it involves an increase in hyperplasia (see paragraph bridging p. 29-30 of the reply).

Therefore, for the reasons of record and the reasons reiterated above, the rejection is maintained because an undue amount of additional experimentation is required in order for one of ordinary skill in the art to be able to use the method to treat or prevent any pathological state of the kidney.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
January 11, 2003